Summary Of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Oxytocin 3 I.U. HEXAL®
3 I.U./ml solution for injection or concentrate for solution for infusion

Oxytocin 5 I.U. HEXAL®
5 I.U./ml solution for injection or concentrate for solution for infusion

Oxytocin 10 I.U. HEXAL®
10 I.U./ml solution for injection or concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin 3 I.U. HEXAL
One ampoule with 1 ml solution for injection or concentrate for solution for infusion contains 3 I.U. oxytocin

Oxytocin 5 I.U. HEXAL
One ampoule with 1 ml solution for injection or concentrate for solution for infusion contains 5 I.U. oxytocin

Oxytocin 10 I.U. HEXAL
One ampoule with 1 ml solution for injection or concentrate for solution for infusion contains 10 I.U. oxytocin

Other excipient(s) with known effect: 8.5–10 mg sodium chloride per ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Use before delivery:
- inducing labour for medical reasons at term
- primary and secondary weak contractions
- stimulating contractions (oxytocin challenge test)

Use after delivery:
- bleeding prophylaxis after miscarriage
- prophylaxis of severe postpartum bleeding
- facilitation and acceleration of the detachment and expulsion of the placenta
- prophylaxis and treatment of subinvolution of the uterus (when the uterus fails to return to its normal size) postpartum
- atonic bleeding in the postpartum period: For this indication, oxytocin should only be used as the agent of second choice if other uterine contracting substances such as methylergometrine, prostaglandins or their derivatives are contraindicated or not tolerated.

4.2 Posology and method of administration

Oxytocin should only be used when strongly indicated for medical reasons, only in hospital and only under

medical supervision. Careful monitoring of the birth (CTG, blood pressure and pulse of the mother) is required for the individual dosage.

Method of administration
Oxytocin HEXAL is administered as an intramuscular injection or as an intravenous infusion.

Posology and duration of administration

Induction of labour for medical reasons at term, primary and secondary weak contractions
To induce labour or strengthen contractions, Oxytocin HEXAL must only be administered as an intravenous continuous infusion and never as a subcutaneous, intramuscular or intravenous single injection.

Oxytocin HEXAL is administered as an intravenous drip or, preferably, using an infusion pump with variable speed. For the drip, 1 I.U. Oxytocin should be diluted in 100 ml of an isotonic sodium chloride solution.

The initial infusion rate should be 0.5–2 x 10^{-3} I.U./min., i.e. 0.05 to 0.2 ml, corresponding to 1–4 drops/min. Depending on the labour, the dosage can be increased in steps at intervals of no less than 15 minutes by 1–2 x 10^{-3} I.U./min until there is a contraction pattern comparable to spontaneous labour. At term or shortly before, this is often achieved with an infusion of less than 10 x 10^{-3} I.U./min. (1 ml, corresponding to 20 drops/min.). If contractions are normal, the infusion volume should not be further increased. The maximum recommended infusion rate is 20–30 x 10^{-3} I.U./min. (2 to 3 ml, corresponding to 40–60 drops/min.).

If regular contractions of the uterus still have not started after the infusion of 500 ml (5 I.U.), the attempt to induce labour should be stopped. Generally, it can be attempted again the following day.

During the whole duration of infusion, the frequency, strength and duration of contractions and the foetal heart rate must be monitored closely. Once appropriate contractions have been achieved, the infusion rate can be reduced. In the case of excessive contractions and/or signs that the placenta is not providing enough oxygen or nutrients (“foetal distress”), the infusion should be stopped immediately.

During a caesarean section after delivery of the child
Immediately after extraction of the child, 5 I.U. can be administered as an infusion (30 x 10^{-3} I.U./min.) as prophylaxis.

Postpartum period (atonic bleeding)

5–10 I.U. I.M. or 5–6 I.U. as an infusion.

Due to the antidiuretic effect of Oxytocin HEXAL (see section 4.8), the following measures should be taken when administering Oxytocin HEXAL in high doses:
An isotonic sodium chloride solution (not glucose) should be used, and the volume of fluid infused should be kept low. At the same time, oral intake should be limited and the fluid balance should be monitored. If a disturbed electrolyte balance is suspected, serum electrolytes should be monitored.

For evacuation after miscarriages
3–6 I.U. oxytocin as I.V. infusion or I.M.

Special patient groups

Renal impairment
No studies in patients with renal impairment are available.

Hepatic impairment
No studies have been carried out on patients with hepatic impairment.

Children and adolescents
No studies have been carried out with children and adolescents.

Elderly patients
No studies have been carried out with elderly patients (65 years or older).

4.3. Contraindications

- hypersensitivity to the active substance or one of the other excipients listed in section 6.1
- hypertensive labour
- "foetal distress" (unless this is immediately before the birth)

All conditions relating to the foetus or the mother due to which spontaneous labour must be avoided and/or vaginal delivery is contraindicated, e. g.:

- an obstacle to birth (e.g. head is too large for the pelvis)
- abnormal foetal position (e.g. breech presentation)
- placenta praevia (placenta in front of/at the internal opening of the cervix)
- vasa praevia
- placental abruption (placenta separates early)
- umbilical cord is looped around the baby or comes out before the baby
- threat of uterine rupture
- polyhydramnios
- preeclampsia (a disease specific to pregnancy characterised by high blood pressure, protein in the urine and fluid accumulation in the tissue)
- tendency to tetanic uterine contraction (sustained contraction of the uterus)
- undilated cervix
- threat of foetal asphyxia (acute serious lack of oxygen for the child due to insufficient oxygenation)

Oxytocin must not be used within 6 hours after vaginal administration of prostaglandins (see section 4.5).

4.4 Special warnings and precautions for use

Oxytocin should not be used for prolonged periods in patients with weak contractions who do not respond sufficiently to oxytocin or in patients with severe cardiovascular problems.

Oxytocin should not be administered as an intravenous bolus injection, as this can lead to acute short-term hypotension associated with erythema and reflex tachycardia.

Cardiovascular disorders
Oxytocin should be administered with caution in patients who are predisposed to myocardial ischaemia due to a pre-existing cardiovascular disorder (e.g. hypertrophic cardiomyopathy, valvular disease and/or ischaemic heart disease, including vasospasm of the coronary arteries) in order to avoid significant fluctuations in blood pressure and heart rate.

QT syndrome
Oxytocin should be administered with caution in patients with known long QT syndrome or related symptoms and in patients who take medicinal products that can lead to QT interval prolongation (see section 4.5).

If oxytocin is used to induce labour or strengthen contractions:

- Oxytocin must only be administered as an intravenous infusion and never as a subcutaneous, intramuscular or intravenous bolus injection.

- *Foetal distress and foetal death:* An overdose of oxytocin may lead to hyperstimulation of the uterus, which can lead to foetal distress, foetal asphyxia and the child's death, or it can result in hypertensive

contractions, tetanic uterine contraction, or uterine rupture. Careful monitoring of the foetal heart rate and the uterus activity (frequency, strength and duration of contractions) is necessary to adjust the dosage to the patient's response.

- *Special monitoring of both mother and child is required in the case of:*
  - previous gynaecological surgeries with opening of the cavity of the uterus, e. g. myomectomy
  - more than four previous births
  - multiple births in older women
  - borderline cephalo-pelvic disproportion (baby's head too big for the mother's pelvis)
  - secondary weak contractions
  - mild to moderate pregnancy-related hypertension or heart disease
  - patients more than 35 years old
  - caesarean section in the lower uterine segment in the medical history

- *Disseminated intravascular coagulation:* In individual cases, the pharmacological induction of labour using uterotonics, including oxytocin, can increase the risk of postpartum disseminated intravascular coagulation (DIC). This risk is connected with the pharmacological induction of labour in itself and not the substance used. The risk is especially increased if the woman has additional risk factors for DIC, such as being 35 or older, complications during the pregnancy and a gestational age of more than 40 weeks. In these women, oxytocin and/or an alternative medicinal product should be used with caution and the doctor should look out for signs of DIC.

Water intoxication
Since oxytocin has a mild antidiuretic effect, high-dosage intravenous continuous infusion in combination with a high fluid intake, which can occur during the treatment of the start of miscarriage, missed miscarriage or postpartum bleeding, can lead to water intoxication, associated with hyponatraemia. The antidiuretic effect of oxytocin in combination with the intravenous administration of fluids may lead to fluid overload, which can cause a haemodynamic form of acute pulmonary oedema without hyponatraemia. To avoid these rare complications, the following precautions should be taken if high oxytocin doses are administered over a long period: An infusion solution containing electrolytes (not glucose) must be used, while the volume of fluid administered intravenously must be kept low (by means of an infusion of oxytocin with a higher concentration than the dose recommended for inducing labour and/or strengthening contractions in case of delivery at term). At the same time, the oral fluid intake must be reduced and the fluid balance monitored. If a disturbed electrolyte balance is suspected, serum electrolytes should be monitored.

Renal impairment
Special care should be taken with patients with severe renal impairment because potential water retention and oxytocin accumulation can occur (see section 5.2).

Intrauterine foetal death
In the case of intrauterine foetal death and if meconium is present in the amniotic fluid, hyperactive (increased) labour must be avoided due to the risk of amniotic fluid embolism.

The limit of 16 x 10^{-3} I.U./min. should only be exceeded for a short time as provocation of hyperbilirubinaemia (increased levels of blood in bilirubin, a bile pigment) in the child due to prolonged high dosage cannot be ruled out with certainty. Furthermore, infant retinal haemorrhage is very common in overactive labour.

Oxytocin HEXAL should not be used parenterally at the same time as products for supporting breast milk production that contain oxytocin.

The administration of Oxytocin HEXAL after prolonged labour may be associated with a possible tendency to seizures in the infant.

Oxytocin HEXAL contains sodium, but less than 1 mmol (23 mg) sodium per ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions that mean concomitant administration is not recommended:

Prostaglandins and their analogues
Prostaglandins and their analogues support myometrium contraction, meaning that oxytocin can potentiate the effect of prostaglandins and their analogues, and vice versa (see section 4.3). An interval of six hours is recommended as the minimum between application of prostaglandin and the subsequent oxytocin application.

Medicinal products for prolonging the QT interval
Oxytocin should be considered a potential arrhythmogenic, particularly in patients with further risk factors for torsades de pointes, such as medicinal products that prolong the QT interval, or in patients with a history of long QT syndrome (see section 4.4).

The uterus-contracting effect of oxytocin is increased by methylergometrine.

Interactions to take into consideration
Inhalation anaesthetics
Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and cause marked weakening of the tone of the uterus, which can reduce the uterotonic effect of oxytocin.

Vascoconstrictors/sympathomimetics
Oxytocin can increase the vasoconstrictor effects of vasoconstrictors and sympathomimetics, including local anaesthetics.

Caudal anaesthetics
When administered during or after a caudal blockade, oxytocin can increase the hypertensive effect of sympathomimetic vasoconstrictors.

4.6 Fertility, pregnancy and lactation Pregnancy

Based on the long-term experience with this substance, its chemical structure and its pharmacological properties, according to the current state of knowledge, no foetal malformations are anticipated if used appropriately.

Breast-feeding
Oxytocin can pass into breast milk in low quantities. However, no harmful effects on the newborn are anticipated as the medicinal product passes into the digestive tract, where it is rapidly inactivated.

Fertility
Not applicable to oxytocin due to the given indications.

4.7 Effects on ability to drive and operate machinery

Not applicable.

4.8 Adverse reactions

In the case of intravenous administration of oxytocin to induce labour or strengthen contractions, an overdose of oxytocin may lead to hyperstimulation of the uterus, leading to foetal distress, foetal asphyxia and the child's death, or it can result in hypertensive contractions, tetanic uterine contraction, or uterine rupture.

In the case of a rapid intravenous bolus injection of oxytocin in doses of multiple I.U., there may be acute short-term hypotension in conjunction with erythema and reflex tachycardia (see section 4.4). These rapid haemodynamic changes can lead to myocardial ischaemia, especially in patients with pre-existing cardiovascular disorders. In the case of a rapid intravenous bolus injection of oxytocin in doses of multiple I.U., there can also be a QTc prolongation.

In rare cases (i.e. incidence of < 0.0006), the pharmacological induction of labour using uterotonics, including oxytocin, can lead to an increased risk of postpartum disseminated intravascular coagulation (DIC) (see section 4.4).

Water intoxication

Water intoxication in connection with maternal and/or neonatal hyponatraemia have been reported in cases where high oxytocin doses were administered together with large electrolyte-free volumes of fluid over a prolonged period (see section 4.4).

The antidiuretic effect of oxytocin in combination with the intravenous administration of fluids may lead to fluid overload, which can cause a haemodynamic form of acute pulmonary oedema without hyponatraemia (see section 4.4).

The following adverse reactions have been reported, independent of the method of administration.

Adverse reactions (table 1, table 2) are listed in accordance with the MedDRA system organ classes and according to their frequency, starting with the most frequent:

Very common (≥1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be assessed based on available data)

The adverse reactions listed in the following table are based on clinical study results and reports after market launch. The adverse reactions from experience with oxytocin after market launch come from spontaneous case reports and reports from the literature. Since these reactions are voluntarily reported from a population of unknown size, their frequency cannot be reliably determined. These reactions are therefore listed under the category "Not known"

Table 1 Adverse reactions in the mother

Immune system disorders		
	Uncommon:	Allergic reactions
	Rare:	Anaphylactic/anaphylactoid reactions associated with dyspnoea, hypotension or shock
Nervous system disorders		
	Common:	Headache
Cardiac disorders		
	Common:	Tachycardia, bradycardia
	Uncommon:	Arrhythmia
	Not known:	Myocardial ischaemia, prolongation of the QT interval
Vascular disorders		
	Common:	Increase in blood pressure
	Not known:	Pronounced fall in blood pressure, especially in the case of a rapid intravenous injection (postpartum)
Gastrointestinal disorders		
	Common:	Nausea, vomiting
Skin and subcutaneous tissue disorders		
	Rare:	Rash, erythema
	Not known:	Angioedema
Renal and urinary disorders		
	Very rare:	Reduced water excretion, water intoxication, maternal hyponatraemia (possible consequences: cerebral oedema, seizures and coma)
Pregnancy, puerperium and perinatal conditions		
	Very common:	Contractions that are too strong with occasional tetanic uterine contraction and resulting hypoxia in the child (lack of oxygen)
	Not known:	Uterine rupture
Respiratory, thoracic and mediastinal disorders		
	Not known:	Acute pulmonary oedema
General disorders and administration site conditions		
	Not known:	Flushing
Blood and lymphatic system disorders		
	Rare:	Disseminated intravascular coagulation

Table 2 Adverse reactions in the foetus/newborn

Pregnancy, puerperium and perinatal conditions		
	Not known:	Foetal distress, foetal asphyxia and death
Metabolism and nutritional disorders		
	Not known:	Hyponatraemia of the newborn

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

Bundesinstitut für Arzneimittel und Medizinprodukte
[Federal Institute for Drugs and Medical Devices]
Abt. Pharmakovigilanz [Pharmacovigilance Dept.]
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

4.9 Overdose

The symptoms and consequences of an overdose are described in sections 4.4 and 4.8. Furthermore, placental detachment and/or amniotic fluid embolism have been reported as a result of uterine overstimulation.

Treatment

First measure in the case of an overdose - accompanied by sustained contraction of the uterus (tetanic uterine contraction) - is to stop the oxytocin infusion. The woman giving birth should be administered oxygen. In the case of water intoxication, the fluid intake must be restricted, diuresis promoted and the electrolyte balance corrected, and any seizures monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: neurohypophysial hormones ATC code: H01BB02

Oxytocin is a cyclic, fully synthetic nonapeptide. This synthetic form is identical to the naturally occurring hormone that is stored in the neurohypophysis and released into systemic circulation in response to breast-feeding and contractions. Oxytocin stimulates the smooth musculature of the uterus more toward the end of pregnancy, during labour and immediately after birth. In this time the number of specific oxytocin receptors in the myometrium increases. Oxytocin receptors are G-protein coupled receptors. Activation of the receptors by oxytocin elicits a release of calcium from the intracellular reservoir and this induces uterine contraction. Oxytocin provokes rhythmic contractions of the lower segment of the uterus, comparable in frequency, strength and duration to those during labour. Due to its synthetic origin, oxytocin contains no vasopressin, but in its pure form oxytocin has a weak specific vasopressin-like antidiuretic effect.

Based on *in-vitro* studies, the prolonged use of oxytocin causes a desensitisation of oxytocin receptors, likely due to the down-regulation of the oxytocin binding site, the destabilisation the oxytocin receptor mRNA and the internalisation of oxytocin receptors.

5.2 Pharmacokinetic properties
Absorption
Oxytocin is ineffective after oral intake.

In I.M. use oxytocin reaches the blood stream within minutes. Oxytocin plasma levels in pregnant women at their due date who received 4 milli-units per minute administered as an intravenous infusion were 2–5 micro-units/ml.

Distribution

The steady-state volume of distribution determined in 6 healthy men after I.V. injection is 12.2 l or 0.17 l/kg. Plasma protein binding is insignificant for oxytocin. It passes through the placenta in both directions. Oxytocin may pass into breast milk in very small quantities.

Biotransformation
Oxytocinase is a glycoprotein aminopeptidase, which is produced during pregnancy and released into the plasma. It can degrade oxytocin. It is produced by both the mother and the foetus. The liver and kidneys play a large role in the metabolism and the clearance of oxytocin from the plasma.
The liver, kidneys, and the systemic circulation therefore contribute to the biotransformation of oxytocin.

Elimination
The plasma half-life of oxytocin is 3 to 20 minutes. The metabolites are excreted in the urine, while less than 1% of oxytocin is excreted unchanged in the urine. The metabolic clearance rate is 20 ml/kg/min in pregnant women.

Renal impairment
No studies have been conducted in patients with renal impairment. However, in consideration of the excretion of oxytocin and its reduced excretion in the urine due to its antidiuretic properties, a possible accumulation of oxytocin can result in the case of prolonged use.

Hepatic impairment
No studies have been conducted in patients with hepatic impairment. Pharmacokinetic changes in patients with hepatic impairment are unlikely, because metabolising enzymes and oxytocinase are not limited to the liver alone and the oxytocinase levels in the placenta at the due date are significantly increased. Therefore, hepatic impairment may not cause any substantial changes in the metabolic clearance of oxytocin.

5.3 Preclinical safety data
Preclinical data for oxytocin based on conventional single-dose studies of acute toxicity, genotoxicity and mutagenicity do not reveal any special risk for humans.
An *in-vitro* study on the genotoxicity and mutagenicity of oxytocin is available. All examinations in human peripheral lymphocyte cultures were negative both in terms of chromosomal aberrations as well as sister chromatid exchange. The mitotic index did not change. Oxytocin has no genotoxic properties. However, the genotoxic potential was not determined *in vivo*.

Carcinogenicity, teratogenicity, and reproduction toxicity
The treatment of rats at an early stage of pregnancy with doses sufficiently higher than the maximum recommended dosage in humans led to embryo loss in one study. No standardised teratogenicity, reproductive toxicity or carcinogenicity studies have been conducted with oxytocin.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Acetic acid 10%
Sodium chloride
Water for injection

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products, apart from those listed in section 4.2.

6.3 Shelf life
3 years

Shelf life after opening the container or after producing the ready-to-use preparation:
The solution is only intended for one-time extraction. The ready-to-use solution must be used immediately. Any remaining unused product must be discarded.

6.4 Special precautions for storage

Store in the refrigerator (2–8°C).

After opening or preparing the ready-to-use diluted solution for infusion:
The chemical and physical stability of the ready-to-use diluted solution for infusion in PE bags and in glass bottles has been determined at 4°C and 25°C for 72 hours.

From a microbiological viewpoint, the ready-to-use preparation should be used immediately, or stored for a maximum of 24 hours at 2–8°C, unless the method of dilution rules out the risk of microbial contamination. If the ready-to-use preparation is not used immediately, the user is responsible for the duration and conditions of storage.

6.5 Nature and contents of the containers
Clear glass ampoules

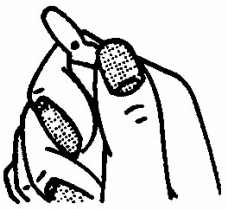
Pack of 10 ampoules of 1 ml solution for injection

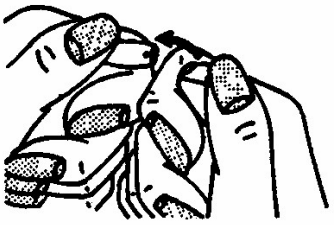
6.6 Special precautions for disposal and other handling
Unused medicinal product or waste material should be disposed of according to national regulations.

Note
Handling the OPC (one point cut) ampoules - It is not necessary to score the ampoule with a file:

Coloured tip pointing upward.
Allow the solution in the neck of the ampoule to flow down by tapping or shaking.

Break the neck of the ampoule backwards from the tip.





7. MARKETING AUTHORISATION HOLDER

Name: Sandoz GmbH,Kundl
Address: Biochemiestrasse 106250.
Country: Austria.

8. MARKETING AUTHORISATION NUMBERS

To be confirmed

9. DATE OF FIRST AUTHORISATIONS

To be confirmed

10. DATE OF REVISION OF THE TEXT

September 2018

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription